OBSTETRICS

Maternal periodontal disease, systemic inflammation, and risk for preeclampsia

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OBJECTIVE: Maternal periodontal disease, a chronic oral infectious and inflammatory disorder, is associated with an increased risk for preeclampsia. Our objective was to determine the relationship between maternal periodontal disease, maternal systemic inflammation, and the development of preeclampsia.

STUDY DESIGN: A secondary analysis of data from the Oral Conditions and Pregnancy Study was performed. A cohort of healthy pregnant women enrolled at less than 26 weeks underwent an oral health examination, serum sampling, and delivery follow-up. Periodontal disease was categorized clinically as present or absent. Maternal serum was assayed for C-reactive protein by high-sensitivity enzyme-linked immunosorbent assay and stratified as elevated ($\geq$ 75th percentile) or not elevated ($<$ 75th percentile). Preeclampsia was defined as blood pressure $>$ 140/90 mmHg and at least 1+ proteinuria on a catheterized urine specimen. Risk ratios (RR) for preeclampsia were calculated, stratified by periodontal disease and C-reactive protein level.

RESULTS: Thirty-one (4%) of 775 women with complete data developed preeclampsia. Women with CRP $\geq$ 75th percentile were more likely than those with CRP $<$ 75th percentile to develop preeclampsia (7% vs 3%, $P < .03$; RR, 95% CI 2.2, 1.1-4.4). Women with periodontal disease and CRP $\geq$ 75th percentile were at increased risk for preeclampsia (adjusted RR 5.8, 1.2-26.9), compared to women without periodontal disease and either CRP $<$ 75th or $\geq$ 75th percentile.

CONCLUSION: Maternal periodontal disease with systemic inflammation as measured by C-reactive protein is associated with an increased risk for preeclampsia.

Key words: C-reactive protein, inflammation, periodontal disease, preeclampsia, pregnancy

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Periodontal disease is a common oral infection, with prevalence ranging from 10-60%.[1] Periodontal disease refers to both gingivitis and periodontitis. Gingivitis is an inflammatory condition of the soft tissues surrounding the teeth and periodontitis involves the destruction of the supporting structures of the teeth, such as the periodontal ligament and bone.[2] Localized increases in the numbers and tissue invasion of certain bacteria, primarily Gram-negative organisms, cause persistent inflammation and destruction of the tissues supporting the teeth.[2,3] Recent data suggest that periodontal disease is also associated with systemic diseases, such as atherosclerotic cardiovascular disease and ischemic stroke.[4-6] Animal data further support these associations. For example, in a murine model of atherosclerosis, a chronic low-grade *Porphyromonas gingivalis* infection accelerates atherogenic plaque progression.[6] In these animal models and in humans, the systemic egress of periodontal bacteria and subsequent inflammatory responses are potential links between periodontal disease and systemic disease.[4]

Periodontitis has also been implicated in adverse pregnancy outcomes, as recently reviewed by Xiong.[1] We previously reported that women with moderate-severe periodontal disease at delivery or disease progression during pregnancy are at increased risk for preeclampsia.[7] This observation has also been reported by several other investigators[8-10]; however, the underlying mechanism of this association is unknown.

Periodontal disease leads to a moderate systemic inflammatory response, and in individuals with periodontal disease, serum antibody titers for specific pathogens, such as *Porphyromonas gingivalis*, are elevated and independently associ-

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ated with elevated C-reactive protein levels.[11,12] Systemic inflammation is one possible link between periodontal disease and preeclampsia, as preeclampsia is associated with endothelial activation and vascular inflammation.[13] C-reactive protein level is a nonspecific marker of inflammation and is higher among pregnant compared to nonpregnant women. Other research has illustrated median C-reactive protein levels during pregnancy center around 3 mg/L throughout all 3 trimesters, with no values above 15 μ/L.[14]

We hypothesize that chronic exposure to oral pathogens leads to both systemic inflammation and preeclampsia, and that systemic inflammation may be one possible explanatory variable in this relationship. In this study, we investigated the relationship between maternal periodontal disease, maternal systemic inflammation, and preeclampsia risk.

Materials and Methods

We performed a secondary analysis of the data from the Oral Conditions and Pregnancy Study (OCAP). The OCAP study was a prospective cohort study of maternal periodontal disease and obstetric outcomes performed by the University of North Carolina School of Dentistry Center for Oral and Systemic Disease, in collaboration with Duke University Medical Center. Institutional Human Subjects approval was obtained to conduct the study. A detailed description of the study has been published previously.[7] In brief, healthy pregnant women were enrolled prior to 26 weeks' gestation. Women were excluded from the study if they were younger than 18 years of age without a legal guardian, were greater than 26 weeks' gestation at enrollment, had a multiple gestation, chronic hypertension, pregestational diabetes, heart murmur or heart valve disease, history of fenfluramine-phentermine use (unless a normal echocardiogram was documented), any medical condition requiring antibiotic prophylaxis for dental treatment, human immunodeficiency virus infection, or delivery that was planned at another medical center. Maternal demographic and medical history data were obtained by patient questionnaire at their initial visit. Details on the course of the pregnancy, labor and delivery, and the newborn were abstracted from the medical record and entered into the Oral Conditions and Pregnancy Study database (Microsoft Access, 1997 SR2, Microsoft, Redmond, WA). An oral health examination was performed and maternal blood was collected at antepartum enrollment and at delivery. Preeclampsia was categorized as 2 episodes of blood pressure greater than 140/90 mmHg, and at least 1+ proteinuria on a catheterized urine specimen.

We previously defined periodontal disease status as either health, mild, or moderate/severe, based on clinical criteria.[7] However, for this analysis, we combined mild and moderate/severe categories because of our primary interest in identifying the contribution of elevated CRP or inflammation as related to the presence or absence of periodontal disease. Therefore, periodontal disease was categorized as either present or absent at enrollment. The absence of periodontal disease was defined as absence of gingival pocket depths greater than or equal to 4-mm pocket depth and absence of gingival pocket depths greater than 3 mm that also bled on probing. Periodontal disease was defined as 1 or more tooth sites with greater than or equal to 4-mm pocket depth or 1 or more tooth pockets greater than 3 mm that bled on probing.

Maternal serum was analyzed at enrollment for C-reactive protein using a high-sensitivity enzyme-linked immunosorbent assay (VIRGO C-Reactive Protein Kit, Hemagen Diagnostics, Waltham, MA). The technique of this assay has been published elsewhere.[16] The range of this assay is 0.5-50 μg/mL. For the purposes of this analysis, serum quartile levels of CRP greater than or equal to the 75th percentile, which correspond to $>$ 15 μg/mL, were defined as elevated.[14] Subsequent to this analysis, these numbers were validated by Belo.[14]

Bivariate analysis was performed on a priori candidate confounders to determine association with the development of preeclampsia using the χ^2 or Student t test. Confounders were variables that changed the association between periodontal disease and preeclampsia by 5% or more. All confounding variables were included in a multivariable logistic regression model. Smoking history was also included in the model. Risk ratios (RRs) and 95% confidence intervals (CI) for risk of preeclampsia were determined by stratifying periodontal disease as present or absent and CRP $\geq$ 75th and $<$ 75th percentile. All analyses were performed using Statistical Analytical Systems 8.0 (SAS Institute, Cary, NC).

Results

One thousand twenty women were enrolled in the OCAP study and considered for this analysis. Of these women, 775 (76%) had both oral health exam results and serum C-reactive protein results. No significant differences were found in age, race, parity, marital status, gestational age, tobacco use, insurance status, periodontal disease, and preeclampsia between women with and without serum C-reactive protein results (data not shown).

Maternal demographic characteristics and obstetric data are illustrated in Table 1. Thirty-one (4%) developed preeclampsia. Women with preeclampsia were similar to those without preeclampsia. The mean and median values of C-reactive protein for women with preeclampsia tended to be higher than those without preeclampsia (35.0 $\pm$ 28.9 vs 17.7 $\pm$ 25.0 μg/mL; $P < .07$ and 8.5 (4.1-30.5) vs 4.7 (0.6-15.2) μg/mL; $P < .07$). Women with C-reactive protein $\geq$ 75th percentile at enrollment were significantly more likely to develop preeclampsia compared to women with C-reactive protein $<$ 75th percentile (6.7% vs 3.1%; $P < .03$; RR, 95% CI, 2.2, 1.1-4.4).

Crude risk ratios for preeclampsia among women with C-reactive protein level $\geq$ 75th percentile, periodontal disease, and the combination of both exposures are illustrated in Table 2. Adjusted risk ratios stratified by the presence of periodontal disease and level of C-reactive protein are shown in Table 3. Among women with periodontal disease, the presence of a C-re-